REMARKS

Amendments to the Specification

Applicants have amended the specification so that the claim to priority is the first sentence of the application. No new matter has been introduced by way of this amendment.

Status of the Claims

Claims 24-159 and 285-305 are pending. Claims 118-135 have been withdrawn from consideration.

The dependencies of claims 45, 47, 50 and 53-55 were amended in Applicants' provisional election of September 28, 2001 due to the constraints of the Restriction requirement of August 28, 2001. The amendments of the dependencies of claims 45, 47, 50 and 53-55 are no longer necessary in light of the Examiner's reconsideration of the restriction. Thus, Applicants have amended claims 45, 47, 50 and 53-55 herein effectively to "undo" the amendments of September 28, 2001. No new matter has been introduced by way of amendment.

Applicants have amended claims 40, 72, 88, 104, 136, and 148 to recite that the claimed polynucleotides encode polypeptides that bind Fas ligand. Additionally, Applicants have deleted the limitation "wherein % identity is determined using the Bestfit program" from claims 40 and 72. Applicants reserve the right to pursue the subject matter of claims 40, 72, 88, 104, 136, and 148 as filed (i.e., as the claims read prior to the amendments requested herein) in one or more divisional or continuing applications. Support for these amendments may be found, for example at page 43, lines 5-14 and page 43, line 35 to page 44, line 3. Thus, no new matter has been introduced by way of amendment.

Information Disclosure Statements

The Examiner indicated in Item 3 of Paper No. 19 that the Information Disclosure Statement, the accompanying list of references as well as copies of the references filed June 21, 2000 are missing from the Patent Office files for the present application and requested that Applicants resubmit these documents. Accordingly, Applicants submit herewith a copies of the Information Disclosure Statement Pursuant to 37 C.F.R. §1.56,

the Form PTO-1449 and references AA-AF, each of which were originally submitted on June 21, 2000.

The Examiner also indicated in Item 3 of Paper No.19 that the Information Disclosure Statement as well as copies of the references filed June 22, 2001 are missing from the Patent Office files for the present application and requested Applicants resubmit these documents. To Applicants knowledge, no Information Disclosure Statement was filed by Applicants on June 22, 2001. Applicants suspect the Examiner meant to refer to the Information Disclosure Statement and accompanying references that were filed on February 22, 2001 and (resubmitted on June 13, 2001). To comply with the Examiner's request, Applicants submit herewith copies of the Information Disclosure Statement Pursuant to 37 C.F.R. §1.56, the revised Form PTO/SB/08 and references AG – BB, each of which were originally submitted on February 22, 2001, and resubmitted on June 13, 2001.

In addition to the two Information Disclosure Statements referred to above, Applicants also submitted an Information Disclosure Statement on October 8, 1998 in the present application. No mention of this Information Disclosure Statement was made in Paper No. 19. Nonetheless, for completeness, Applicants have also resubmitted copies of the Information Disclosure Statement Pursuant to 37 C.F.R. §1.97(b), the Form PTO-1449 and the references cited therein, each of which was originally submitted on October 8, 1998.

Applicants also note that submitted herewith is a (new) Third Supplemental Information Disclosure Statement, with Revised form PTO/SB/08 and copies of references BC-BH.

Drawings

The Examiner indicated in Item 4 of Paper No.19 that no substitute drawing of Figure 2 (comprising Figures 2A and 2B) had been received, but that substitute drawings of Figures 3 and 4 had been received on June 13, 2001 (in the resubmission of papers filed by Applicants on February 22, 2001).

The substitute Figures 2A and 2B to which the Examiner is referring were originally filed on June 21, 2000 with the Submission of Formal Drawings containing

Figures 1, 2A-B, 3A-P, and 4-6. Subsequently, Applicants resubmitted corrected formal drawings of Figures 3A-P and 4 on February 22, 2001 (resubmitted June 13, 2001).

To ensure the Patent Office is in receipt of the correct Formal Drawings of all figures in the present application, Applicants submit herewith a complete set of Formal Drawings containing copies of Figures 1, 2A-B, 5 and 6 as filed on June 21, 2000 and figures 3A-P and 4 as filed on February 22, 2001 (resubmitted June 13, 2001).

Claim Rejections under 35 U.S.C. §§101 and 112

For the record, Applicants note that the outstanding rejections under 35 U.S.C. §§101 and 112 in the present application (see below) were essentially addressed and overcome for the reasons stated below in a child application (09/518,931 filed March 3, 2000) which claims priority to the present application.

The Claimed Polynucleotides have Utility under 35 U.S.C. §101

The Examiner has rejected claims 24-117, 136-159, and 285-309 under 35 U.S.C. §101 for allegedly not being supported by either a specific and substantial utility or a well-established utility.

The Examiner acknowledges that the specification teaches that the polynucleotides of the invention encode members of the Tumor Necrosis Factor Receptor Family that the polypeptides of the inventions can be used diagnostically or therapeutically to treat diseases or disorders including graft versus host disease. The Examiner continues by stating:

> The assertion that the nucleic acids and/or proteins of the instant invention can be used in the diagnosis or treatment of diseases or disorders is not a specific and substantial utility and is based on the assumption that the proteins are receptors in the tumor necrosis factor receptor family, which as a family are involved in myriad biological pathways and activities....there is no nexus between any of the diseases or disorders and the molecules of the instant invention. Given no disease state or any other function or activity known for the proteins, the proteins are not considered to have utility. (Paper No. 19, pages 5-6)

Applicants respectfully disagree. The claimed polynucleotides have a specific and substantial utility, for example, in the preparation of polypeptides which can be used for treatment of graft vs. host disease. This utility is clearly disclosed in the specification in

the fourth paragraph on page 6. (This disclosure is also found in the earliest application to which the present application claims priority, namely Application Serial No. 60/035,496 filed January 14, 1997, in the second full paragraph on page 7).

This utility has been confirmed, for example, by Zhang et al., *Journal of Clinical Investigation* 107:1459 (2001), reference BH on the Revised form PTO/SB/08 submitted herewith), who show that TR6-Fc treatment reduces symptoms in a murine model of graft vs. host disease. The Federal Circuit held in *In re Brana*, evidence dated after the filing date "can be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement already in the specification." 51 F. 3d. 1560, 1567 at n19 (Fed. Cir. 1995). Such evidence "goes to prove that the disclosure was in fact enabling when filed (*i.e.*, demonstrated utility)." *Id., citing In re Marzocchi*, 439 F2d. at 224 n.4, 169 U.S.P.Q. at 370 n.4.

Applicants emphasize that the asserted utility in the present application is adequate under all applicable authority. At the very least, Applicants' priority application contains an assertion of utility, unlike the situation in *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (1966), in which no utility was asserted at all. Further, Applicants' asserted utility is a specific, substantial and credible utility and not a "throw away" utility (such as using a composition for landfill) as defined in the current United States Patent and Trademark Office's Utility Guidelines.

The Claimed Invention is Adequately Enabled under 35 U.S.C. §112, First Paragraph

The Examiner rejects claims 24-117, 136-159 and 285-305 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement.

More specifically, the Examiner states that

> Since the claimed invention is not supported by either a specific and substantial utility or a well established utility...one skilled in the art clearly would not know how to use the claimed invention. Even if the specification were enabling of how to use the TNFR-6α nucleic acid or polypeptide, enablement would not be found commensurate in scope with the claims.

Applicants believe the first part of this rejection regarding the allegation that the claimed invention is "not supported by either a specific and substantial utility or a well

established utility" has been overcome by Applicants arguments above defending the utility of the claimed invention, for example, in the treatment of graft versus host disease.

The second part of this rejection under 35 U.S.C. § 112, first paragraph, pertains to the Examiner's assertion that even knowing the utility of the claimed polypeptides, a skilled artisan would not know how to make and use polynucleotides that are at least 90%, or at least 95%, identical to: the polynucleotide of SEQ ID NO:1, the polynucleotide of the cDNA contained in clone HPHAE52, a polynucleotide encoding the polypeptide of SEQ ID NO:2; a polynucleotide encoding the polypeptide encoded by the cDNA contained in clone HPHAE52; or to fragments of the aforementioned polynucleotides. Applicants respectfully disagree. However, in the interest of facilitating prosecution in the present application, Applicants have amended claims 40, 72, 88, 104, 136, and 148 to recite that the claimed polynucleotides encode polypeptides that bind Fas ligand. Applicants believe that the addition of this functional limitation overcomes the present rejection under 35 U.S.C. § 112, first paragraph. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Availability of Deposited Plasmids

The Examiner states that the Enablement of claims 56-87, 104-117 and 148-159 requires availability of the specific sequence claimed therein, and, therefore, a deposit of clone HPHAE52 should have been made in accordance with M.P.E.P. Chapter 2400 and 37 C.F.R. §§ 1.801-809. In order to satisfy this requirement, Applicants direct the Examiners attention to the disclosure of the first paragraph of the Detailed Description spanning pages 8-9.

Additionally, the undersigned attorney of record in the present application hereby states that the plasmid HPHAE52, deposited under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure and accorded ATCC Deposit Number 97768, will be irrevocably and without restriction, except for the limitations allowed by 37 C.F.R. § 1.808(b), released to the public upon the issuance of a patent containing claims reciting said plasmid for the present application.

Applicants believe that all the requirements of 37 C.F.R. §§ 1.801-809 have been met with respect to the deposited plasmid recited in the claims.

CONCLUSION

In view of the foregoing remarks, Applicants believe that this application is now in condition for allowance, and an early notice to that effect is urged. The Examiner is invited to call the undersigned at the phone number provided below if any further action by Applicant would expedite the examination of this application.

Finally, if there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for in the Petition for an Extension of Time submitted concurrently herewith, such an extension is requested and the appropriate fee should also be charged to our Deposit Account.

Respectfully submitted,

Date: March 19, 2002

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KKH/MS/vsr
Enclosures

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Gentz et al. Art Unit: 1646

Application Serial No.: 09/006,352 Examiner: O'Hara, E.

Filed: January 13, 1998 Attorney Docket No.: PF454

Title: Tumor Necrosis factor 6α and 6β

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Amendments are shown in bold with insertions indicated with underlining and deletions indicated by strikeout.

In the Specification:

The paragraph spanning lines 13-15 of page 1 has been deleted.

The following paragraph has been inserted after the title "Field of the Invention" on page 1:

This application claims benefit of 35 U.S.C. section 119(e) based on copending U.S. Provisional Application Serial No. 60/035,496, filed January 14, 1997, which is hereby incorporated herein by reference.

In the Claims:

Claims 40, 45, 47, 50, 53-55, 72, 88, 104, 136, and 148 have been replaced with the following amended claims:

40. (Once Amended) An isolated nucleic acid molecule comprising a nucleotide sequence encoding a first amino acid sequence at least 90% identical to the entire length of a second amino acid sequence selected from the group consisting of:

(a) amino acid residues 1 to 300 of SEQ ID NO:2;

(b) amino acid residues 2 to 300 of SEQ ID NO:2;

(c) amino acid residues 31 to 300 of SEQ ID NO:2; and

(d) amino acid residues 31 to 283 of SEQ ID NO:2;

wherein ~~% identity is determined using the Bestfit program~~ **a protein consisting of said first amino acid sequence binds Fas ligand**.

45. (Twice Amended) The nucleic acid molecule of claim **44** ~~43~~ encoding a first amino acid sequence at least 95% identical to a second amino acid sequence according to **(d)** ~~(c)~~.

47. (Twice Amended) The nucleic acid molecule of claim **44** ~~45~~ that comprises a nucleotide sequence heterologous to SEQ ID NO:1.

50. (Twice Amended) A recombinant vector comprising the nucleic acid molecule of claim **44** ~~45~~.

53. (Twice Amended) A recombinant host cell comprising the nucleic acid molecule of claim **44** ~~45~~ operably associated with a regulatory element that controls expression of said nucleic acid molecule.

54. (Twice Amended) A method of producing a polypeptide encoded by the nucleic acid molecule of claim **44** ~~45~~ comprising:

(a) culturing a host cell comprising said nucleic acid molecule under conditions suitable to produce said polypeptide; and

(b) recovering said polypeptide from the culture.

55. (Twice Amended) A composition comprising the nucleic acid molecule of claim **44** ~~45~~ and a pharmaceutically acceptable carrier.

72. (Once Amended) An isolated nucleic acid molecule comprising a nucleotide sequence encoding a first amino acid sequence at least 90% identical to the entire length of a second amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of the full-length polypeptide encoded by the cDNA contained in clone HPHAE52 as deposited with the ATCC as accession number 97810;

(b) the amino acid sequence of the full-length polypeptide, lacking the N-terminal methionine, which is encoded by the cDNA contained in clone HPHAE52 as deposited with the ATCC as accession number 97810;

(c) the amino acid sequence of the mature polypeptide encoded by the cDNA contained in clone HPHAE52 as deposited with the ATCC as accession number 97810; and

(d) the amino acid sequence of the soluble extracellular domain of the polypeptide encoded by the cDNA contained in clone HPHAE52 as deposited with the ATCC as accession number 97810;

wherein ~~**% identity is determined using the Bestfit program**~~ **a protein consisting of said first amino acid sequence binds Fas ligand**.

88. (Once Amended) An isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence encoding amino acid residues m-300 of SEQ ID NO:2, where m is an integer in the range of 1 to 49;

(b) a nucleotide sequence encoding amino acid residues 1-y of SEQ ID NO:2, where y is an integer in the range of 193 to 300;

(c) a nucleotide sequence encoding amino acid residues m-y of SEQ ID NO:2, where m is an integer in the range of 1 to 49 and y is an integer in the range of 193 to 300; and

(d) a nucleotide sequence that is the complement of (a), (b), or (c)**;**

wherein a protein consisting of said amino acid residues bind Fas ligand.

104. (Once Amended) An isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence encoding a polypeptide comprising a portion of the complete amino acid sequence encoded by the cDNA clone contained in ATCC Deposit 97810 wherein said portion excludes up to 48 amino acids from the amino terminus of the complete amino acid sequence;

(b) a nucleotide sequence encoding a polypeptide comprising a portion of the complete amino acid sequence encoded by the cDNA clone contained in ATCC Deposit 97810 wherein said portion excludes up to 107 amino acids from the carboxy terminus of the complete amino acid sequence;

(c) a nucleotide sequence encoding a polypeptide comprising a portion of the complete amino acid sequence encoded by the cDNA clone contained in ATCC Deposit 97810 wherein said portion excludes up to 48 amino acids from the amino terminus and up to 107 amino acids from the carboxy terminus of the complete amino acid sequence; and

(d) a nucleotide sequence that is the complement of (a), (b), or (c))**;**

wherein said polypeptide consisting of a portion of the complete amino acid sequence encoded by the cDNA clone contained in ATCC Deposit 97810 binds Fas ligand.

136. (Once Amended) An isolated nucleic acid molecule comprising a nucleotide sequence encoding at least 30 contiguous amino acids of SEQ ID NO:2 **wherein a protein consisting of said contiguous amino acids binds Fas ligand**.

148. (Once Amended) An isolated nucleic acid molecule comprising a nucleotide sequence encoding at least 30 contiguous amino acids of the complete amino acid sequence encoded by the cDNA contained in clone HPHAE52 as deposited with the ATCC as accession number 97810 **wherein a protein consisting of said contiguous amino acids binds Fas ligand**.